Clinico-pathological Conference

AIDS related primary intrathoracic lymphoma

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Case report (*Dr C P Cottrill*)
The patient, a 34 year old Caucasian woman who worked as a clerical officer presented in February 1988 requesting repeat HIV antibody testing. A week previously she had been told she was HIV antibody positive at another hospital. Tests had been suggested because of persistent facial rash. Further enquiry revealed that the patient was exclusively heterosexual and had no history of intravenous drug use. She had two male partners in the last year and neither was known to be an intravenous drug user or bisexual. Her only past history was of laser treatment for cervical dysplasia in June 1987. After counselling the repeat HIV antibody test was carried out and was positive. Dermatological assessment showed the facial rash to be due to seborrhoeic dermatitis and rosacea. In the mouth there was oral hairy leucoplakia on the tongue. The patient remained well until December 1988 apart from intermittent oral candida. She then presented with a two week history of dysphagia without weight loss. Examination of the mouth revealed oral candida and hairy leucoplakia. A barium swallow showed oesophageal candida fulfilling the criteria for the diagnosis of AIDS. A blood count at this stage showed a haemoglobin of 15·4 g/dl, a total white count of $4·4 \times 10^9$/l (lymphocytes $1·0 \times 10^9$/l, platelets 154×10^9/l). The P24 antigen was positive with a level of 76 pg/ml.

The patient was started on zidovudine 250 mg four times daily together with primary prophylaxis against *Pneumocystis carinii* pneumonia with co-trimoxazole 960 mg daily and fluconazole 50 mg daily for her oesophageal candidiasis.

In January 1989 the patient was admitted with a three day history of non-productive cough, dyspnoea and fever. Examination revealed her to be pyrexial and there were coarse crackles audible over the left upper zone. The chest radiograph showed mild bilateral, upper and midzone shadowing. Blood gases drawn whilst breathing room air showed a PO_2 of 9·8 kPa. A sample of sputum induced by inhalation of hypertonic saline was negative for *Pneumocystis carinii*, mycobacteria and other pathogens. At fibreoptic bronchoscopy no endobronchial abnormality was noted and bronchoalveolar lavage was also negative showing inflammatory exudate only. Blood cultures were also negative. It was felt the patient had an atypical pneumonia and she was treated with oral erythromycin and flucloxacillin in conventional doses. There was rapid clinical recovery but the radiograph was slow to improve taking six weeks to return to normal.

Over the next ten months until December 1989 the patient remained well taking zidovudine, co-trimoxazole and fluconazole. At the end of 1989 she reported discomfort in her arms and legs, particularly on exercise. Examination showed that she had proximal loss of muscle bulk together with proximal weakness, there was no muscle tenderness. Investigations included a serum creatine kinase (CK) level of 59 (normal < 170 IU/l) and an electromyogram which showed no evidence of myositis. The zidovudine was continued. Over the next 14 months the patient's clinical condition remained stable. There was no deterioration in her muscle weakness although the CK became abnormally raised, ranging from 262 to 537 IU/l. Full blood count taken in May 1990 showed a haemoglobin of 11·3 g/dl, a white count of 2·2 with a total lymphocyte count of $0·5 \times 10^9$/l.

In January 1991 the patient was admitted with a one week history of flu-like illness with night sweats, anorexia, lethargy and fever. In addition, she reported right sided headache and a brief episode of blurred vision in the left eye. On examination she was pyrexial (39°C) and had bilateral shotty axillary lymphadenopathy but there were no signs of meningism nor focal neurology; fundoscopy was normal. CT of the brain was normal and a lumbar puncture showed no white cells, a protein of 0·45 g/dl and a CSF/plasma glucose ratio of 2·4/5·8 mmol/l. Toxoplasma and syphilis antibody tests and cryptococcal antigen were all negative in both cerebrospinal fluid and blood. Serum biochemistry and liver function tests were normal. Hepatitis B serology was negative. Cultures of urine and stool were negative and initial reports of blood culture were negative also. A chest radiograph was performed and showed a mass adjacent to the left hilum thought to be due to lymphadenopathy, the lung fields were clear (fig 1). The patient's headache improved spontaneously but her fever and night sweats continued. She was allowed home to have outpatient CT of the chest which showed a thick walled cystic lesion containing fluid in the apical segment of the left lower lobe. A CT guided aspiration biopsy yielded a blood clot only; culture of this was negative. Shortly after CT was performed the patient was electively readmitted as prolonged culture of her blood had grown *Mycobacterium*

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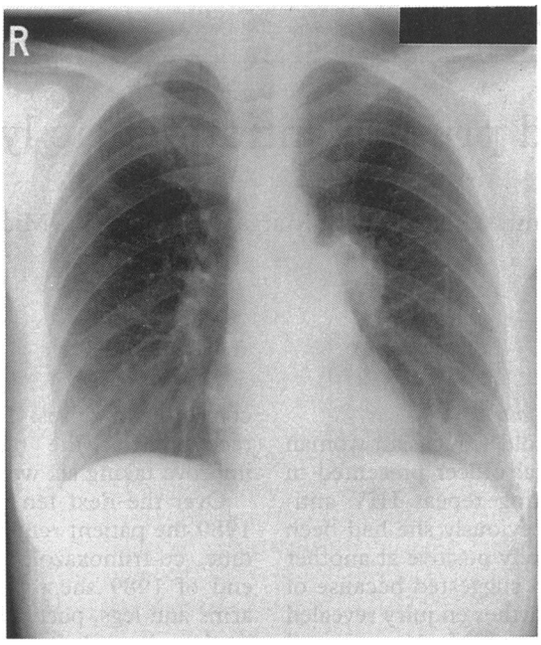

Figure 1 Chest radiograph showing "left hilar mass".

avium intracellulare. The patient still had fever and night sweats and was anorexic. By now she weighed only 50 kg (weighed 65 kg at original presentation in February 1988). She was treated with a combination of amikacin 7·5 mg/kg intravenously once daily for 14 days together with oral ethambutol 800 mg daily, ciprofloxacin 500 mg twice daily and rifampicin 600 mg once daily. She was given 14 days amikacin as induction and was discharged home taking oral ethambutol, ciprafloxacin and rifampicin together with megestrol which was started as an appetite stimulant, zidovudine, co-trimoxazole and fluconazole. The patient remained clinically stable over the next two months apart from an anaemia of 8·9 g/dl, this was attributed to zidovudine therapy and the dose was reduced to 250 mg twice daily.

She was readmitted in April 1991 with increasing cough productive of small quantities of purulent sputum, exertional dyspnoea, lethargy, night sweats and central chest pain. She had been compliant with treatment for MAI and had also taken co-trimoxazole and fluconazole. On examination she had a low grade pyrexia of 37·5°C, there was no lymphadenopathy; in the chest the percussion note was impaired at the left base with absent breath sounds. There was 2 cm hepatomegaly but no splenomegaly. The patient had lost a further kilogram in weight. A chest radiograph showed left lower lobe collapse. Repeat CT of her chest was performed, this showed collapse of the left lower lobe with concentric narrowing and obliteration of the left lower lobe bronchus (fig 2). No lymphadenopathy or tumour was seen in the mediastinum and the remaining lung fields were clear. Fibreoptic bronchoscopy was performed, this showed a normal trachea, carina and right bronchial tree. On the left side the left main bronchus was normal but the left lower lobe bronchus was completely obstructed with a sputum plug. This was easily aspirated and revealed a white necrotic polypoid tumour, which was biopsied. Histology revealed necrosis, fibrosis and chronic inflammation but no evidence of tumour. A rigid bronchoscopy was then performed under general anaesthetic, the findings were that the main carina was normal and mobile, the left main bronchus appeared narrowed by extrinsic compression. Biopsies were performed of the tumour in the left lower lobe bronchus, which revealed non-Hodgkins lymphoma (fig 3). The tumour was high grade and of B cell origin. There was evidence of kappa light chain restriction.

Staging investigations included an abdominal ultrasound which was normal, a bone marrow aspirate and trephine, which apart from showing slightly hypocellular appearances revealed no evidence of lymphoma or of *Mycobacterium avium intracellulare* infection. In view of the patient's weight loss, poor perform-

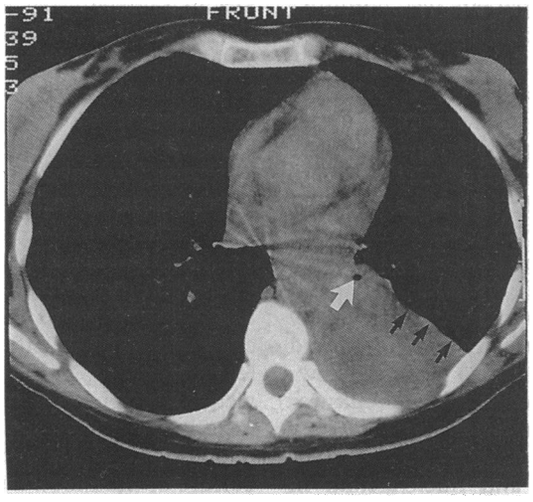

Figure 2 CT scan of thorax showing left lower lobe collapse (black arrows) and concentric narrowing of the left lower lobe bronchus (white arrow).

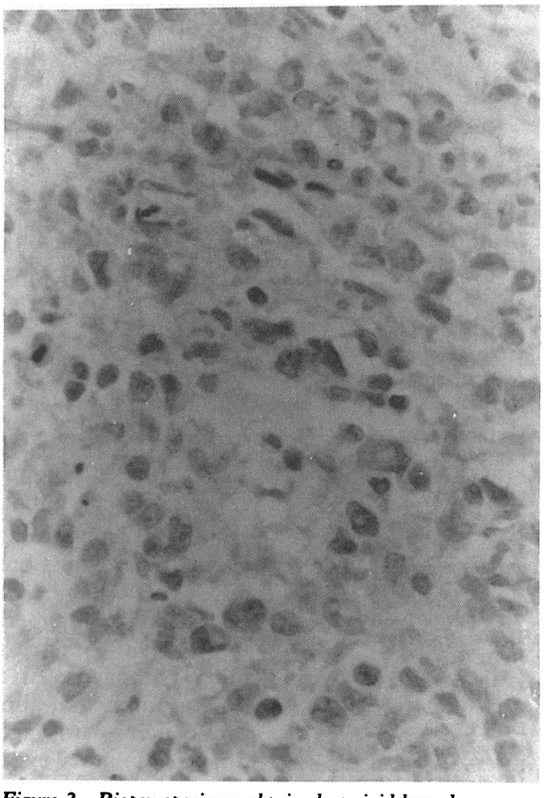

Figure 3 Biopsy specimen obtained at rigid bronchoscopy from the left lower lobe bronchus. Magnification × 400; haematoxylin and eosin.

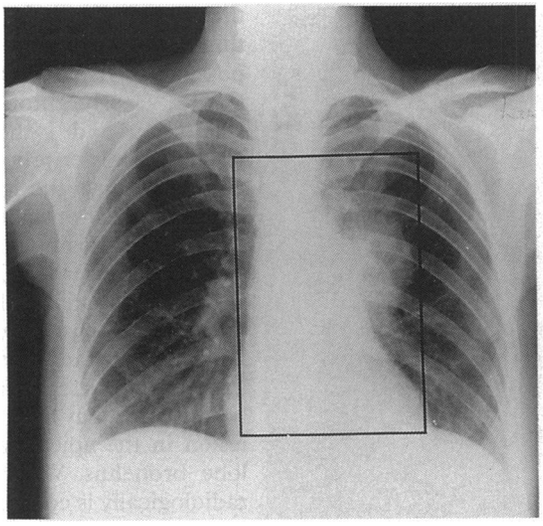

Figure 4 Chest radiograph showing superimposed radiotherapy field (within area of black box).

ance status and the fact that she had a previous AIDS defining diagnosis together with intercurrent *Mycobacterium avium intracellulare* infection it was felt that the aim of treatment would be palliation and not cure. In addition, staging investigations suggested only localised disease. The priority was to rapidly palliate the cough and exertional dyspnoea and to prevent the permanent left lower lobe re-collapse. She was treated with involved field radiotherapy (fig 4). The dose of radiotherapy was 30 Gy given in 10 fractions over 12 days by opposing fields. The patient tolerated the treatment well and was discharged home. However, she was admitted two weeks later with severe radiation oesophagitis and was unable to eat or drink. She required temporary nasogastric feedings, her symptoms settled and she was subsequently able to eat and drink again normally.

Over the next two months she remained mildly dyspnoeic on exertion. Her cough then returned and persisted despite a course of antibiotics. A repeat chest radiograph taken at this stage showed no change in the hilar mass but there were new changes attributed to radiotherapy in the left upper zone (fig 5). When reassessed at the end of August 1991 the patient had a monophonic fixed inspiratory and expiratory wheeze audible throughout the chest. There was a firm 3 cm mass palpable in the right axilla and the patient was thought clinically to have progressive disease. She was readmitted for investigation. At bronchoscopy tumour was seen obstructing the trachea reducing its diameter by 60%. The tumour began 8 cm below the vocal cords and was concentric. The lower extent of the tumour was at the level of the carina. The carina itself was widened but both left and right main bronchi were normal in appearance; there was no abnormal vasculature in the left main bronchus which may have been expected following radiotherapy. A fine needle aspiration biopsy of the right axillary mass did not show any tumour. Despite the negative result it was felt the axillary mass was pathologically involved so a single 6 Gy fraction of radiotherapy was given to this region in addition to further radiotherapy to the mediastinum, 15 Gy in five fractions. With this treatment the patient's symptoms of cough and dyspnoea improved significantly and so she was allowed home. Over the next two weeks her general condition deteriorated with further weight loss and a recurrence of night sweats despite regular oral dexamethasone. In addition, her cough returned and she had mild dysphagia. She was readmitted following acute loss of voice together with a worsening of dyspnoea. Nasendoscopy showed the right vocal cord was thickened with tumour, the larynx was not obstructed. Palliative chemotherapy was given with a single dose of 2 mg of vincristine. The patient was then discharged home to the joint care of her general practitioner and the Bloomsbury Community Care Team. She was admitted once more just prior to her death with increasing and distressing dyspnoea. She was treated symptomatically with helium and oxygen mixture and opiates. She died at the end of October 1991, five and a half months from the date of the original diagnosis of lymphoma. A post mortem examination was performed.

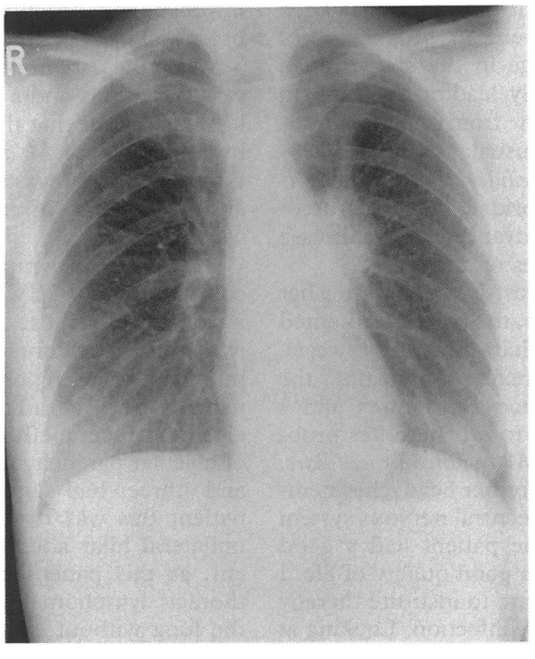

Figure 5 Chest radiograph following radiotherapy showing that the "hilar mass" is unchanged.

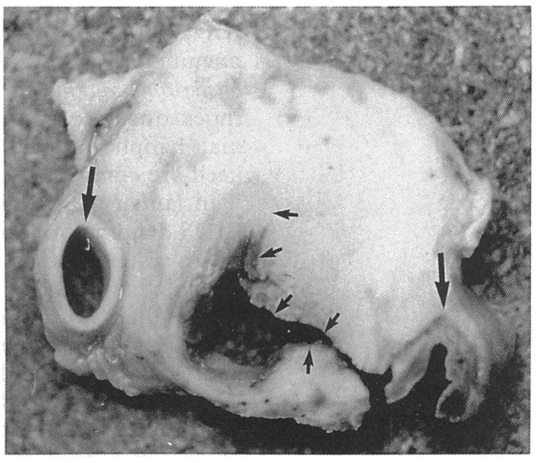

Figure 6 Macroscopic appearances of the tracheal tumour at necropsy. The tumour (short arrows) has markedly reduced the lumen of the trachea. The carotid arteries are seen either side of the trachea (long arrows).

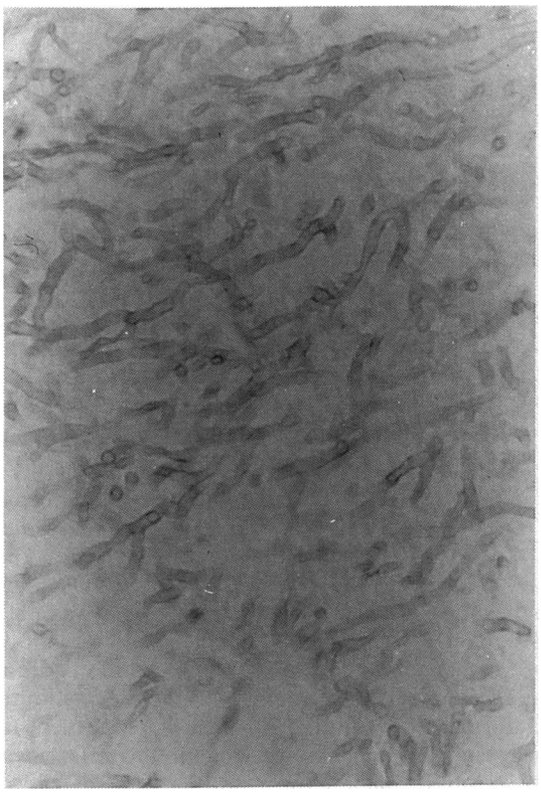

Figure 7 Section through the tracheal tumour showing hyphae of aspergillus. Magnification × 400; Haematoxylin and eosin.

Discussion (*Professor J Moxham*)

This is a very unusual case. The patient experienced her AIDS defining illness in 1988, and by the time she presented with *Mycobacterium avium intracellulare*, she was clearly profoundly immunosuppressed. Her total lymphocyte count was so low that it was not possible to count the number of T helper cells. It is important to understand that this women's prognosis was poor at the time that she presented with lymphoma, because she was already two years down the line from her original AIDS defining diagnosis.

In the mid 1980s there was a marked improvement in the prognosis for AIDS patients due to prophylaxis against *Pneumocystis carinii* pneumonia and also the introduction of zidovudine. Since that time there has been little further improvement in prognosis but there has been a change in the spectrum of complications, ultimately leading to death in AIDS patients.[1] Death from pneumocystis pneumonia is now unusual, whereas *Mycobacterium avium intracellulare*, chronic diarrhoea due to cryptosporidia, Kaposi's sarcoma, lymphoma and advanced HIV disease itself are common causes of death.

In January 1991, almost two years after her AIDS defining diagnosis, the patient presented with a systemic illness, characterised by sweats, fever, lethargy and anorexia. At that time the patient had no respiratory symptoms and I think it was reasonable to attribute her problems to infection with *M avium intracellulare*. Extensive investigation for her headaches demonstrated no important central nervous system disease. At this time the patient had a good performance score and a good quality of life. I am sure it was appropriate to institute therapy for *M avium intracellulare* infection. Looking at the chest radiograph (fig 1) I am not sure that this showed a bulky left hilum at all. It is possible to visualise the left side of the mediastinum clearly through the apparent hilum shadowing and I therefore think that there must be a posteriorly placed pulmonary lesion projecting onto the left hilum. A lateral chest radiograph is not available but I would assume that the shadowing was in the apical segment of the left lower lobe. I note that subsequent CT demonstrated a thick walled cystic lesion in the apical segment of the left lower lobe and I wonder whether it would have been better to have bronchoscoped the patient at this stage because this may have identified an obstructing lesion in the apical segment of the left lower lobe bronchus. What I think we are seeing radiologically is collapse and consolidation and subsequent cavitation. I was interested to note that CT demonstrated that the left hilum was normal and that the mediastinum was free of adenopathy and tumour. I think that the subsequent complete collapse of the left lower lobe caused the cavitated area to disappear as the whole left lower lobe lost volume.

When the cystic lesion had been noted on the CT scan a fine needle aspiration biopsy was performed but I think it is relatively common for this investigation to not provide a diagnosis for cystic lesions, particularly when there is little fluid within them.

The idea that there may have been an obstructing lesion in the apical segment of the left lower lobe at a relatively early stage leads me to reconsider whether the symptoms that were initially attributed to *M avium intracellulare* infection may have been due to pulmonary problems. The patient certainly did very well following therapy for *M avium intracellulare* and I note that only one blood culture was positive and that subsequent blood cultures were negative for *M avium intracellulare*. This is rather unusual in disseminated infection and it may be that *M avium intracellulare* was in large measure a "red herring" in terms of explaining her symptoms. The antibiotics used at this time would have been likely to improve any secondary infection, distal to bronchial obstruction.

When the patient developed obvious respiratory symptoms and a collapsed left lower lobe it became clear that these symptoms could not be attributed to *M avium intracellulare* infection. The patient was therefore bronchoscoped and a diagnosis of endobronchial lymphoma was made.

AIDS-related lymphoma, originally a rare complication of HIV disease, is increasing in incidence. In most series of AIDS related lymphoma intrathoracic disease is unusual[2 3] but in a series reported by Sider, 11 of 35 patients had intrathoracic disease, of these eight had pleural effusions, five had interstitial or alveolar parenchymal lung disease or a mass and three had lymphadenopathy (in one patient this was mediastinal, two others had unilateral hilar adenopathy). Clearly to present, as this patient did, with primary intrathoracic lymphoma—defined as lymphoma of the lung without extrathoracic manifestations

within three months—is very unusual. AIDS-related primary intrathoracic lymphoma has previously been reported only rarely[5].

What treatment should have been given to this patient? She had late HIV disease and was very immunosuppressed. You made the decision, and I fully concur with this, that limited staging was appropriate and it was entirely reasonable not to proceed to CT of head and lumbar puncture. The aim clearly was to palliate this woman's symptoms.

When the patient presented with breathlessness and acute loss of voice you found that she had tumour on the vocal cord. This was an important point because if the hoarseness had been due to vocal cord paralysis this would have implied high right sided mediastinal disease. When you rebronchoscoped the patient you found to your surprise that she had severe obstruction of the trachea from 8 cm below the cords right down to the carina. Beyond this the airways appeared normal. Clearly the radiotherapy she had received has been very effective at the site of the original disease, but what is surprising is that she subsequently developed two "skip" lesions, one in the trachea and one on the vocal cord.

To summarise the case; this patient developed AIDS-related intrathoracic lymphoma against the background of profound immunosuppression and advanced HIV disease. I think that relatively early on she probably obstructed the apical segment of the left lower lobe with tumour and subsequently developed collapse consolidation of this segment with cavitation. I think that the culture of *M avium intracellulare* from a single blood culture was not of great relevance but that the antibiotics she then received successfully ameliorated her respiratory symptoms. The patient's lymphoma then spread and the left lower lobe collapsed. It was eventually appreciated that she had tumour in the left lower lobe bronchus and following this she received radiotherapy. There was good response to radiotherapy as far as the tumour in the left lower lobe was concerned but she subsequently developed lymphoma in other sites of the respiratory tract. In retrospect, given that the *M avium intracellulare* infection was probably not clinically significant, it may have been more appropriate to have treated this patient's lymphoma with chemotherapy.

Dr M F Spittle

The radiotherapy field used to treat this patient encompassed a wide area around the tumour and included the mediastinum well above the disease visible clinically at the time of bronchoscopy (fig 4). There was no supracarinal disease seen at bronchoscopy and CT, which showed left lower lobe collapse and narrowing of the left lower lobe bronchus, confirmed there were no involved lymph nodes within the mediastinum, nor tumour in this area. She was treated with local irradiation as she had local disease only and this treatment would not prejudice her already poor clinical condition.

Chemotherapy is the usual treatment of the aggressive and widespread B cell lymphomas that occur in AIDS[3], but radiotherapy is useful for such local manifestations. This patient had severe mucositis secondary to her radiotherapy which is well described in HIV positive patients and is not yet explained. It seems to occur particularly in patients of poor performance status and at a dose which would not normally provoke this response. Lymphomas are usually radiosensitive and would be expected to respond well to this amount radiotherapy, as happened in this case. Sometimes we have found recurrent lymphoma to be unexpectedly radioresistant. I have not previously seen this progression of disease with "skip" lesions occurring in the trachea and larynx in a patient with lymphoma either with or without HIV infection.

This patient's general condition was extremely poor throughout the period of her diagnosis of lymphoma. In a study of 100 cases of AIDS related lymphoma treated in this country by the UK AIDS Oncology Group the median survival from presentation is only five months[6]. In this patient both radiotherapy and chemotherapy treatment was problem-orientated and probably did not affect survival. However, it may have improved the quality of her life.

Clinical diagnosis

AIDS-related primary intrathoracic B cell lymphoma.

Necropsy (Dr A Gallimore and Professor L Michaels)

The body was that of a thin and wasted white female. External examination revealed no skin lesions and there was no palpable lymphadenopathy. The features of hairy leukoplakia were noted on the lateral borders of the tongue. The main findings on internal examination were as follows:

In the larynx there was a large, ulcerating tumour extending from the epiglottis to the ventricle. The subglottis was normal, as was the proximal trachea. Lower in the trachea, 8 cm from the cords, there was a circumferential, obstructing tumour which extended almost to the carina (fig 6). The main bronchi appeared normal. Both lungs showed numerous necrotic tumour deposits in all lobes. The largest of these was in the left lower lobe and measured 7 cm in diameter. A thin rim of viable tumour was present at the periphery of the necrotic foci.

The liver was mildly enlarged and congested and there was a solitary tumour deposit in the left lobe, 6 cm in diameter. In the right kidney there was replacement of the lower pole by white, homogenous tumour.

Histological examination demonstrated that the tumorous deposits in the larynx, epiglottis, lung, kidney and liver were of a high grade non-Hodgkins's lymphoma of B-cell type identical to that present in the bronchial biopsy. An unexpected finding was the presence of aspergillus in ulcerated mucosa overlying the tracheal tumour (fig 7). There was no evidence in the lung of infection by *Pneumocystis carini*, mycobacteria, cytomegalovirus or any other infective agent. Hairy leukoplakia of the

tongue was confirmed histologically with the presence of hyperkeratosis, parakeratosis and koilocytosis. Incidental histological findings included the presence of extensive dysplasia of the epithelium lining of the upper respiratory tract, including the larynx and marked oncocytosis of the duct epithelium of mucous glands in the larynx.

Patological diagnosis

1 AIDS-related high grade non-Hodgkin's B-cell lymphoma of the lungs, larynx, trachea, kidney and liver.
2 Hairy leukoplakia of the tongue.
3 Focal invasive apergillosis of the trachea.
4 Widespread epithelial dysplasia of the upper respiratory tract.

Discussion (*Professor J Moxham*)

This woman presented with AIDS-related primary intrathoracic lymphoma and this is very unusual. What is even more unusual is that radiotherapy produced an excellent resolution of the disease in the left lower lobe and yet despite the trachea being included in the original radiotherapy field, the patient developed a skip lesion in the trachea and right vocal cord.

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